REMARKS

The present invention relates to a method of inducing and enhancing the proliferation of human bone marrow stromal cells.

The present Office Action, dated August 10, 2004, indicates that claims 1-29 and 31-36 are pending in the present application. Applicants point out that claim 13 was previously canceled by way of the Amendment dated April 19, 2004. As such, claims 1-12, 14-29 and 31-36 are pending and under examination. The present Amendment serves to address the issues raised by the Examiner with respect to claims 1-12, 13-29 and 31-36 as set forth in the present Office Action.

Applicants have amended claims 1, 16, 24, 31 and 32 herein to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Specifically, claims 1, 16, 24, 31 and 32 have been amended herein to recite that low density replating allows the cells to expand by a factor of at least 10-fold. Support for the amendments to claims 1, 16, 24, 31 and 32 is found throughout the specification. For example, in lines 14-25 on page 21, the specification teaches that the low cell density plating and replating allows for a significant degree (e.g at least 10-fold, 50-fold, 100-fold, 200-fold, 300-fold, or more) in the expansion of a marrow stromal cell population.

Rejection of Claims 1-29 and 31-36 pursuant to 35 U.S.C. §102(b)

The Examiner has rejected claims 1-29 and 31-36 under 35 U.S.C. §102(b). Specifically, the Examiner asserts that Huang et al. (1997 Biotechnology Letters 19:89-92) teaches cell density-dependent proliferation of murine bone marrow-derived stromal cell lines. In addition, the Examiner contends that Huang teaches a method of culturing cells at a 3 day interval by serial passaging the cells and then plating them in 96-wells plates by seeding the cells at 5, 50 and 500 cells per well. Therefore, the Examiner is of the opinion that Huang meets the limitations of the claimed invention. Applicants respectfully submit that Huang does not anticipate the present invention for the following reasons.

It is hornbook law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is

contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). Therefore, Huang must describe each and every element of claims 1-29 and 31-36 in order to anticipate these claims under 35 U.S.C. §102(b), and this reference does not satisfy this requirement.

As indicated in the present Office Action, the Examiner asserts that Huang teaches murine bone marrow-derived stromal cell lines. Applicants respectfully point out that the pending claims of the present application recite a method of inducing proliferation of isolated human marrow stromal cells in vitro. Nowhere does Huang teach using human marrow stromal cells. Huang cannot anticipate the present invention because Huang does not disclose each and every element of the claimed invention. Applicants, in view of the foregoing arguments, respectfully request reconsideration and withdrawal of the rejection of claims 1-29 and 31-36 pursuant to 35 U.S.C. §102(b) as being anticipated by Huang.

Rejection of claims 1-29 and 31-36 pursuant to 35 U.S.C. §103(a)

The Examiner has rejected claims 1-29 and 31-36 under 35 U.S.C. §103(a) as being *prima facie* obvious over Huang et al. (1997 Biotechnology Letters 19:89-92). As discussed above, the Examiner is of the opinion that Huang teaches cell density-dependent proliferation of murine bone marrow-derived stromal cell lines. From this, the Examiner asserts that it would have been *prima facie* obvious for one of skilled in the art to arrive at the claimed invention and the motivation to do so arises from the teachings of Huang. Applicants respectfully traverse this rejection.

The three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP § 2142

The first prong of the *In re Vaeck* test, the requirement that the references themselves or the knowledge in the art must provide some suggestion or motivation, has not been met in this instance. The Examiner states that Huang teaches serial culturing of the cells and then plating them in 96-wells plates by seeding the cells at 5, 50 and 500 cells per well. As an initial matter, Applicants point out that the Examiner has misinterpreted the teachings of Huang. Huang plates the cells at an initial inoculum size of 5, 50, or 500 cell/well in 24-well plates rather than in 96-well plates. Further, with respect to the use of 96-well plates, Huang uses 96-well plates to examine the ability of the cells to proliferate from a single cell, in which it was observed that although the cells grew when the initial density was high, the cells were not able to proliferate from a signal cell after three weeks. Nowhere does Huang teach plating and replating at specific cell densities to arrive at the expansion levels as encompasses in Applicants' claims.

The present invention encompasses a method of inducing and enhancing the proliferation of human marrow stromal cells *in vitro* by plating the isolated cells at low densities in the presence of a growth medium, harvesting the cells, and replating the cells to a second growth surface at a specific density of cells in the presence of a growth medium. As amply detailed in the specification, such as in Example 2, beginning at page 36, the methods presently claimed result in a dramatic increase in the number of population doublings of the cells in the absence of differentiation. Applicants have amended the claims to recite that the low density replating allows the cells to expand by a factor of at least 10-fold. That is, the present invention relates to the unexpected result that contrary to prior art methods for culturing/expanding marrow stromal cells, the low cell density plating and replating methods of the present invention promotes rapid and extensive expansion of a marrow stromal cell population. Further, the claims as pending relate to a method of inducing proliferation of isolated human marrow stromal cells by plating the cells as an initial density of less than about 50 cells per square centimeter and replating the cells at least one time at an initial density of less than about 50 cells per square centimeter. Applicants contend that the teachings of Huang do not provide any suggestion or motivation to arrive at the present invention.

Huang teaches murine bone marrow stromal cells. Nowhere does Huang suggest or motivate the artisan to use human bone marrow stromal cells as encompassed in the pending claims. Even if Huang did teach human bone morrow stromal cells, which Huang does not,

Applicants contend that Huang uses these cells for different purposes from those of the present invention. That is, Huang teaches two methods of generating murine bone marrow stromal cell lines. The first method includes plating 2 X 10^7 murine bone marrow cells to a T-25 tissue culture flask (800,000 cells per square centimeter), then growing them for two weeks, and subjecting the cells to serial passages at a 3-day interval in order to establish stromal cell lines (LC1 and LC2). Nowhere during this first method, for example during the serial passaging of the cells, does Huang teach replating the cells at a defined cell density, yet alone the replating of the cells at the densities as recited in the pending claims to allow the cells to expand by a factor of at least 10-fold. Further, nowhere is there any suggestion that the methods disclosed in Huang et al. would afford an unexpected fold increase in the expansion of the cells. One skilled in the art upon reading Huang et al. would not be motivated to serially passage the cells at a low density to arrive at a heightened increase in cell proliferation as encompassed in the claims. At best, Huang teaches that in a T-25 culture, LC1 and LC2 (the two cell lines out of ten created) "were able to grow to confluence on the T-25 tissue culture flask from an inoculum size as low as $5x10^5$ cells per flask" (page 90, first column). In fact, Huang teaches away from the present invention because Huang requires higher cell densities than recited in the present claims. Nowhere does Huang teach or suggest plating and replating the cells at a low density as recited in the claims to induce the cells to proliferate and expand by a factor of at least 10-fold.

The second method taught by Huang, which relates to the generation of a murine bone marrow stromal cell line, involves treating a bone marrow cell culture with mycophenolic acid (MPA). LC3 was the only cell line successfully generated out of ten cell lines by culturing a bone marrow cell culture in the presence of MPA. LC3 was the single MPA-treated cell line that grew to confluence in T-25 culture "from an inoculum size of $5x10^5$ cells per flask." In any event, the three cell lines generated by Huang (LC1, LC2 and LC3) were plated in 24- or 96-well plates to assess the minimum initial cell density for proliferation. It was first observed that none of these cell lines grew from a single cell culture in 96-well plates. However, it was observed that some of these cell lines were able to grow in 24-well plates to varying degrees, in which the 24 well plate cultures were plated at 5, 50 or 500 cells per well, corresponding to about 2.8, 28 and 280 cells per centimeter squared, respectively. Applicants point out that this is the only time Huang teaches plating the cells at a specific density. However, the present claims included replating cells at a low density to allow the cells to expand by a factor of at least 10-fold. As

more fully discussed below, Huang does not teach low density replating of the cells, yet alone that the replating the cells at the specified densities would induce enhance proliferation and expansion of the cells by a factor of at least 10-fold. Rather, Huang teaches that the initial plating of the cells at these defined cell densities was a "one-time" inoculation step whereby the plated cells were allowed to grow for a period of time in order to evaluate the minimum initial density required to establish colonies. Applicants assert that a "one-time" plating of the cells does not suggest or motivate the artisan to replate the cells.

Further, Applicants point out that Huang was unsuccessful in establishing colonies from the LC1 and LC2 cell lines (non MPA-treated cells) using the "one-time" plating at densities equal to or less than 50 cell per well (in 24 well plates), which amounts to about 28 cells per centimeter squared. At the higher density of 500 cells/well, Huang shows that the LC2 cell line formed only 10 colonies and the LC1 cell line formed an even lower number of colonies. Thus, the results of Huang, at best, demonstrate that the LC1 and LC2 cell lines proliferate following an initial plating of the cells at a density that is higher than the density encompassed in the present claims. For example, the LC1 and LC2 cell lines exhibited proliferation properties when plated at an initial higher density of 500 cells/well (in a 24 well plate), corresponding to about 280 cells per centimeter squared which is not a low density plating in the context of the present application. As such, based upon the teachings of Huang, one skilled in the art would not be motivated to plate non-MPA-treated cells at low densities to promote proliferation, but rather would be motivated to plate non-MPA-treated cells at higher densities than those encompassed in the pending claims to induce enhanced proliferation. Further, as discussed elsewhere herein, the claims relate to low density replating of the cells, which cannot be obvious in view of the fact that Huang teaches a "one-time" plating technique to assess the proliferation potential of the LC1 and LC2 cell lines.

With respect to the MPA-treated LC3 cell line, Huang observed limited colony formation at the lower densities (1 colony at 5 cells/well and 4 colonies at 50 cells/well). However, at the higher density of 500 cells/well (280 cells per centimeter squared), the number of LC3 colonies was increased to 28. Based upon the teachings of Huang, one skilled in the art would recognize that the "one-time" plating of MPA-treated cells at a low density could induce proliferation, but not at a heighten level as encompassed in the pending claims. Rather, Huang teaches that in order to enhance the proliferation of the cells, it is required that the MPA-treated

cells be plated at a higher density than encompassed in the present claims. In any event, Applicants' cells are not treated with MPA, and therefore the teachings of Huang with respect to MPA-treated cells cannot render the present invention *prima facie* obvious.

The Examiner also contends that Huang teaches the use of conditioned medium to culture murine bone marrow-derived stromal cell lines, thereby rendering the present invention *primia facie* obvious. Huang uses conditioned medium to induce proliferation of the three cell lines in an attempt to establish colonies. Condition medium was prepared by incubating the respective cell lines (LC1, LC2 or LC3), which were allowed to be grown to confluence, with basic medium supplemented with 20% heat-inactivated fetal bovine serum. It was observed that the MPA-treated LC3 cell line and to a lesser extend the LC2 cell line was able to proliferate at a seeding density of 50 cells/well (in a 24 well plate) when incubated with conditioned medium, and therefore indicated that conditioned medium contained a soluble growth factor that contributed to the proliferation of the cells. It was also observed that LC1 did not produce any colonies at a seeding density of 50 cells/well (in a 24 well plate) when cultured with any of the conditioned medium. Therefore, based upon these results, Huang indicates that the proliferation of bone marrow stromal cell lines is dependent on growth factors present in the conditioned media in addition to being dependent on a minimum cell density. However, nowhere does Huang suggest the claimed subject matter of replating the cells to arrive at an induced expansion of at least 10-fold. At best, Huang teaches the use of conditioned medium to generate colony formation during non-passage culturing of murine bone marrow stromal cells at initial densities of 50 cells/well (24 well plates) for MPA-treated cells (LC3). As such, the teachings of Huang would motivate one skilled in the art to use conditioned medium over growth medium to enhance the proliferation of the cells without replating the cells at the low densities of the present invention. Again, Huang is deficient with respect to the teachings of replating the cells at a low density to arrive at the heightened proliferation levels as encompasses in the present claims. Applicants assert that not only does Huang not teach replating of the cells, Huang does not teach replating of the cells at the specified cell density that the Examiner has indicated. For example, the Examiner contends that the serial passaging of the cells encompass replating the cells at a specified low density. However, Applicants assert that the Examiner has misinterpreted the reference to encompass replating the cells at the specified cell density of 5, 50 and 500 cell/well (in a 24 well plate). Rather, as discussed above, Huang teaches a "one-time" plating of the cells

at the specified density in order to determine the minimum cell density required to promote proliferation.

Huang teaches away from the present invention because one skilled in the art would be motivated to replate cells at a higher cell density than that recited in the present claims. If the skilled artisan were to follow the teachings of Huang, the skilled artisan would fail and find no further motivation to plate and replate cells at a low density as recited in the claims to increase the expansion of the bone marrow stromal cells. Thus Huang fails to support a *prima facie* case for an obviousness rejection of claims 1-29 and 31-36.

The second prong of the *In re Vaeck* test, the requirement that there be a reasonable expectation of success, is similarly not met in this instance. As detailed above, Huang teaches a minimum initial cell density requirement for the proliferation of murine bone marrow stromal cell line. When based on the teachings of Huang, the skilled artisan at best would be motivated to use only a cell line generated by treatment with MPA. However, the present claims do not encompass using MPA-treated cells because nowhere is MPA disclosed in the as-filed specification. Therefore, a skilled artisan upon reading the present application would not be able to arrive at a MPA-treated cell.

In addition to the requirements set forth above, in order to establish a *prima facie* case of obviousness, the prior art reference(s) must teach or suggest all of the claim limitations. Similar to the other prongs of the *In re Vaeck* test, Huang fails to teach or suggest all of the claim limitations. Huang does not teach or even suggest plating and replating the cells at a density of less than about 50 cells per square to induce enhanced proliferation of bone marrow stromal cells. For all of the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection of claims 1-29 and 31-36 under 35 U.S.C. §103(a).

Rejection of claims 1, 22-29 and 31-36 under 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 22-29 and 31-36 under 35 U.S.C. §103(a) as being *prima facie* obvious over Huang et al., Kuznetsov et al. (Journal of Bone and Mineral Research 12: 1335-1347), Azizi et al. (1998, Proc. Nat'l. Acad. Sci. USA 95: 3908-3913), Greenberger (U.S. Patent No 5,766,950) and Prockop (1997, Science 276: 71-74).

Applicants respectfully thank Examiner Ram R. Shukla for clarifying the present rejection in a telephone conversation dated November 8, 2004 between Quang D. Nguyen,

Ph.D., Registration No. 52,066. Per the telephone conversation, the Examiner indicated that Huang et al. was the primary reference and the remaining references were secondary references with respect to the rejection of claims 1, 22-29 and 31-36 under 35 U.S.C. §103(a) as being *prima facie* obvious. In any event, the Examiner contends that one skilled in the art would have been motivated to add growth factors and conditioned medium to the culture medium for growing human marrow stromal cells. Therefore, the Examiner reasons that it would have been *prima facie* obvious to combine the teachings of these references to arrive at the present invention as recited in claim 1, 22-29 and 31-36. Applicants respectfully submit that these references alone or in combination do not render the present invention *prima facie* obvious for the following reasons.

With respect to Huang, the deficiencies of this reference are discussed above and are not repeated here.

The Examiner contends that Kuznetsov teaches multiple passaging and cell culture medium comprising fetal bovine serum. Thus, the Examiner reasons that the teachings of Kuznetsov in combination with Huang renders the present invention *prima facie* obvious. Applicants disagree with the Examiner for the following reasons.

Kuznetsov merely teaches standard culturing methods for generating a cell population, and therefore the teachings of Kuznetsov cannot correct the deficiencies of Huang. Kuznetsov does not teach replating the cells at a low density as encompassed in the pending claims. Rather, Kuznetsov uses low cell density for the initial plating only for the generation of a clonal cell population. Following the initial low density plating, Kuznetsov uses high density plating that is higher than the density encompassed in the pending claims to maintain high growth characteristics. For example, on page 1337, first paragraph, "cells were plated in 75 or 175 cm^2 flasks at 0.1-0.2 X 10^5 cells per cm^2 and subsequent passages were performed when cells were approaching confluence". Applicants contend that prior art methods using high cell density plating, such as the methods of Kuznetsov, exhibited a much lower degree of cell expansion (e.g., about 3-fold). As such, there is no suggestion of plating the cells at a low density as encompassed in the claims to enhance the proliferation of the cells. Therefore, Kuznetsov in combination with Huang does not render the present invention *prima facie* obvious because Kuznetsov does not correct the deficiencies of Huang.

Applicants respectfully submit that Huang in view of Kuznetsov cannot render

claims 1, 22-29 and 31-36 *prima facie* obvious, and request reconsideration and withdrawal of the Examiner's rejection pursuant to 35 U.S.C. §103(a).

With respect to the rejection of the claims over Huang et al. in view of Azizi et al., the Examiner is of the opinion that Azizi teaches growing human marrow stromal cells in a medium comprising PDGF-AA. Therefore, the Examiner reasons that it would have been *prima facie* obvious to combine the teachings of Huang and Azizi to arrive at the present invention as recited in claims 1, 22-29 and 31-36.

Azizi merely teaches the addition of PDGF-AA to the culture medium in order to increase in the growth rate of marrow stromal cells, and therefore the teachings of Azizi cannot correct the deficiencies of Huang. Azizi teaches the isolation of human MSCs from bone marrow aspirate whereby the MSCs (characterized as adherent cells) are cultured to confluency and plated at a ratio of 1:2 or 1:3. The cells were replated at these ratios for about 3-5 passages, wherein PDGF-AA was added to the cell culture beginning at the second passage in order to induce an increase in the growth rate of the cells. Nowhere does Azizi suggests that decreasing the initial density of isolated MSCs or decreasing the density of harvested MSCs provided to a second growth surface or replating the cells at a low density would further induce proliferation. There is no suggestion of plating the cells at a low density as encompassed in the claims to enhance the proliferation of the cells. Rather, Azizi teaches away from the present invention because Azizi teaches plating the cells at a higher density than the density as recited in the pending claims. Further, Azizi teaches the requirement for the presence of PDGF-AA in the culture medium to induce an enhanced proliferation rate of the cells. As such, the teachings of Azizi do not correct the deficiencies of Huang, and thus Huang when combined with Azizi cannot render the present invention *prima facie* obvious.

Applicants respectfully submit that Huang in view of Azizi cannot render claims 1, 22-29 and 31-36 *prima facie* obvious, and request reconsideration and withdrawal of the Examiner's rejection pursuant to 35 U.S.C. §103(a).

With respect to the rejection of the claims over Huang et al. in view of Greenberger, the Examiner is of the opinion that Greenberger teaches a method for selection and expansion of stromal cells, wherein the cells are grown in a vessel pre-coated with fibroblast growth factor and the cell culture is maintained in the presence of conditioned medium. Therefore, the Examiner reasons that it would have been *prima facie* obvious to combine the

teachings of Huang and Greenberger to arrive at the present invention as recited in claims 1, 22-29 and 31-36. Applicants submit that the combination of Huang and Greenberger cannot render claims 1, 22-29 and 31-36 *prima facie* obvious under 35 U.S.C. §103(a).

The teachings of Greenberger do not correct the deficiencies of Huang. Greenberger merely teaches standard culturing methods for bone marrow stromal cells using conditioned medium. Greenberger states that the conditions used for human cells are those used for culturing canine bone marrow stromal cells. Greenberger indicates that the "key to this regimen of cell culture" (col. 6 lines 30-38) is a gelatin pre-coating of the flask, aFGF, heparin, and returning the non-adherent cells to the culture flask. Greenberger teaches the plating of the cells at a density ranging from 1 X 10^6 to 2.5 X 10^6 cells into T75 flasks. In addition, Greenberger teaches culturing primary bone marrow cells at an initial total number of 2.75 X 10^7 cells and then growing the cells until confluency before replating. The cells are replated at a total number of 2.5 X 10^6 cells. In culturing the human cells, Greenberger used aFGF, gelatin pre-coating, the same plating density and the same expansion techniques as used for canine cell culture. In any event, Greenberger does not teach plating and replating of the cells at a low density as encompassed in the pending claims to induce a heighten proliferation of the cells. As such, the teachings of Greenberger do not correct the deficiencies of Huang, and thus Huang when combined with Greenberger cannot render the present invention *prima facie* obvious.

Applicants respectfully submit that Huang in view of Greenberger cannot render claims 1, 22-29 and 31-36 *prima facie* obvious, and request reconsideration and withdrawal of the Examiner's rejection pursuant to 35 U.S.C. §103(a).

With respect to the rejection of the claims over Huang et al. in view of Prockop, the Examiner is of the opinion that Prockop demonstrates the state of the art of marrow stromal cells, their isolation, characteristics, and growth properties in cell culture (i.e. secreted cytokines and growth factors such as IL-1, IL-6, CSF-1 and CSF). Therefore, the Examiner reasons that it would have been *prima facie* obvious to combine the teachings of Huang and Prockop to arrive at the present invention as recited in claims 1, 22-29 and 31-36. Applicants submit that the combination of Huang and Prockop cannot render claims 1, 22-29 and 31-36 *prima facie* obvious under 35 U.S.C. §103(a).

Prockop merely provides a review of the history of MSCs and teaches the potential uses of MSCs, and therefore does not, in anyway, render the present invention obvious.

That is, Prockop does not disclose the plating and replating at a low density to induce increased proliferation of MSCs. Therefore, the teachings of Prockop do not correct the deficiencies of Huang. Applicants contend that Huang in view of Prockop cannot render the present invention *prima facie* obvious under 35 U.S.C. §103(a), and request reconsideration and withdrawal of the Examiner's rejection pursuant to 35 U.S.C. §103(a).

Further, the rejection of claims 1, 22-29 and 31-36 under 35 U.S.C. §103(a) as being obvious over Huang et al. in view of the combined teachings of Kuznetsov et al., Azizi et al., Greenberger, and Prockop, collectively, does not hold.

The Examiner asserts that it would have been *prima facie* obvious for one of skilled in the art to combine the density-dependent proliferation of murine bone marrow-derived stromal cell lines taught by Huang, with the culture conditions taught by Kuznetsov, with the addition of PDGF-AA taught in Azizi, as well as the conditioned medium taught by Greenberger, and the general properties of MSCs taught by Prockop et al., to arrive at the present invention.

Applicants submit that Huang in view of these references cannot render claims 1, 22-29 and 31-36 *prima facie* obvious under 35 U.S.C. §103(a). As discussed elsewhere herein, Huang cannot stand alone to render the present claims *prima facie* obvious and the combined teachings of Kuznetsov, Azizi, Greenberger and Prockop do not correct the deficiencies of Huang. Specifically, none of the references either alone or combined, teach plating and replating of the cells at a low density of less than about 50 cells per square centimeter of growth surface to induce enhanced proliferation and expansion of the cells by a factor of at least 10-fold. Therefore, the teachings of Kuznetsov, Azizi, Greenberger and Prockop do not correct the deficiencies of Huang.

Applicants, in view of the foregoing arguments, respectfully request reconsideration and withdrawal of the rejection of claims 1, 22-29 and 31-36 pursuant to 35 U.S.C. §103(a) as being *prima facie* obvious.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 1-12, 14-29 and 31-36 are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

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(Date)

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Enclosure: Petition for Extension of Time and fee therefor